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$SnCl_4$-mediated oxidative reaction for formation of binaphthoquinone and dinaphthofuran frameworks and its application to natural product synthesis

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Abstract—A simple method was developed for the direct synthesis of 2,2′-binaphthoquinones and dinaphtho[1,2-*b*;2′,1′-*d*]furans, utilizing an oxidative reaction via electron donor–acceptor complexes of 1-naphthols with $SnCl_4$ in the absence or presence of dioxygen. As an application of this method to natural product synthesis, we describe a facile biomimetic synthesis of several binaphthoquinones, 3,3′-bijuglone, 3,3′-biplumbagin and elliptinone.

The biaryl substructure is a central building block in a very large number of natural products.[1a] Among natural biaryls, binaphthoquinones including 3,3′-bijuglone (**1**), 3,3′-biplumbagin (**2**) and elliptinone (**3**), dinaphthofurans such as balsaminones A, and binaphthols such as michellamine A have been isolated from several plants and show various biological activities.[1] We are interested in the oxidative reactions of 1-naphthols (NAP) in order to develop a method for constructing these biaryl substructures, aiming at biomimetic synthesis of the above natural products. In general, the synthesis of binaphthoquinone and dinaphthofuran frameworks requires two steps, namely, the biaryl coupling of NAP and subsequent oxidation or ring closure of the resulting 2,2′-binaphthols (BNAP). Although a number of authors have obtained the above frameworks in two steps,[2] only few examples of synthesis in one step have been recorded.[3] On the other hand, stannic chloride ($SnCl_4$; SC) is used extensively in organic synthesis as a Lewis acid for enhancing a variety of organic reactions. However, there have been only a few reports to date on oxidative reactions with SC.[4]

In the preceding paper,[5] we reported the direct synthesis of BNAP **5** utilizing the biaryl coupling reaction via the electron donor–acceptor (EDA) complex of NAP **4** with SC. During further investigations to characterize the range of applicability of SC, we have found a novel method for synthesizing 2,2′-binaphthoquinones (**7**; BNAPQ) and also dinaphtho[1,2-*b*;2′,1′-*d*]furans (**8**; DNF) from the corresponding **4** in one-pot by utilizing an oxidative reaction with SC in the presence or absence of dioxygen (O_2). Here, we describe these results, including a possible reaction mechanism, and their application to the biomimetic synthesis of naturally occurring **1**, **2** and **3**.

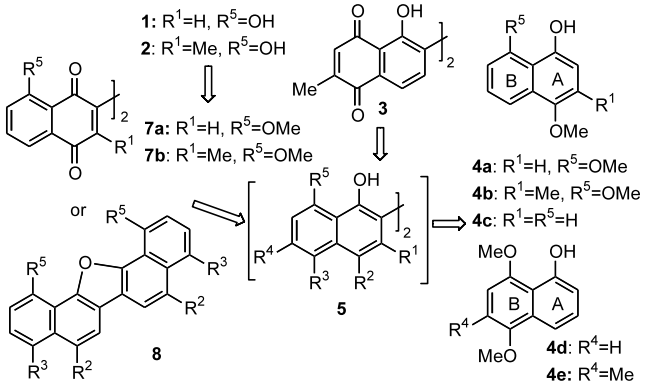

Figure 1.

Firstly, we investigated the reaction of **4**[5,6] with the SC/O_2 system in the presence of O_2 with the aim of achieving a facile synthesis of naturally occurring **1** and **2** under various conditions; the results are shown in Table 1 and Scheme 1. The best yields were obtained when using NAP (1 mmol) with a catalytic amount of

Keywords: naphthoquinones; dinaphthofurans; oxidation; tin and compounds; dioxygen.

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Table 1. Oxidative reactions of naphthols with $SnCl_4$ in the presence of O_2[a]

Entry	Naphthol	Solvent	Temp. (°C)	Time (h)	Product (isolated yield, %)				Recovered (%)
					5	**6**	**7**[d]	**9**[d]	**4**
1	**4a**	CH_2Cl_2	23	1	75	5	–	–	15
2	**4a**	CH_2Cl_2	23	20	–	22	76	–	–
3	**4b**	$MeNO_2$	100	7	52	Trace	–	–	20
4	**4b**	$MeNO_2$	100	71	–	Trace	48	–	–
5	**4d**	$MeNO_2$	100	1	20	–	–	24	33
6	**4e**	$MeNO_2$	100	5	8	–	–	19	53
7[b]	**4a**	CH_2Cl_2	23	48	82	4	2	–	8
8[b]	**4d**	$MeNO_2$	100	1	20	–	–	16	47
9[b]	**4e**	$MeNO_2$	100	5	5	–	–	–	60
10[c]	**5a**	CH_2Cl_2	23	1.5	49	37	7	–	–
11	**5a**	CH_2Cl_2	23	0.5	41	46	1	–	–

[a] General procedure: the reactions of naphthols (1 mmol) with $SnCl_4$ (0.25 equiv.) were carried out using dioxygen (O_2)-saturated solvent in a sealed tube with stirring under normal laboratory light. Similar results were obtained in the dark.
[b] This reaction was carried out with $TiCl_4$ (0.25 equiv.) in place of $SnCl_4$ under the same conditions as above.
[c] With 30% H_2O_2 (1 mmol) in place of dioxygen.
[d] Structures **9** were elucidated by analyses of IR, ^1H, ^{13}C NMR spectra, with the aid of 2D NMR spectral analyses, and transformation to the corresponding **10**.

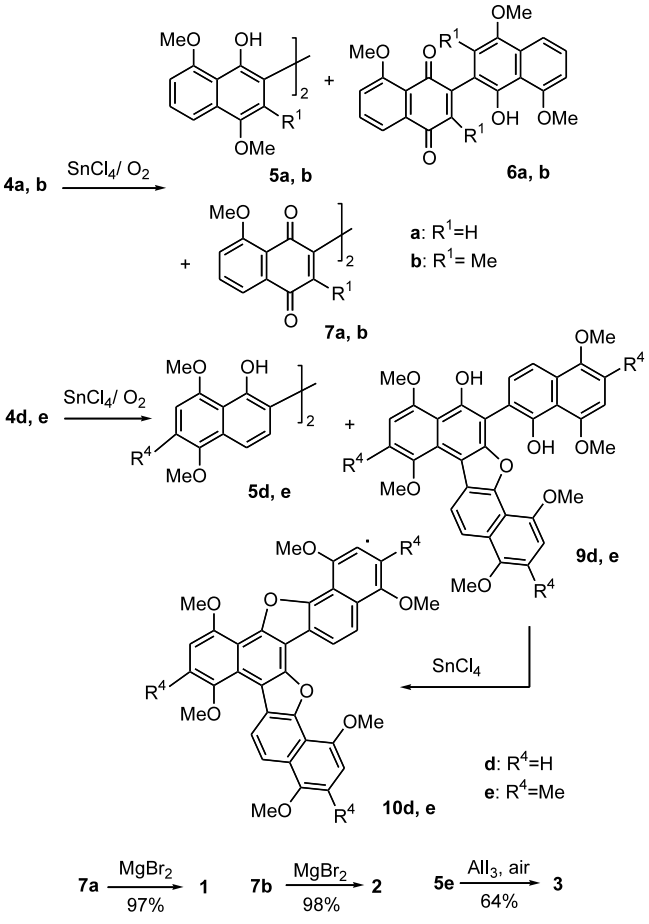
SC (0.25 equiv.) in all cases. We found that the nature of the major products changed drastically with the passage of time at room temperature. In the cases of **4a–b**, BNAP **5a–b** were obtained as major products in the reaction for a short time (1–7 h) (entries 1, 3). Prolonged reaction (60–75 h) under the same conditions selectively afforded BNAPQ **7a–b**, synthetic intermediates to the desired natural products, in one-step from **4a–b** (entries 2, 4). The reaction of **4a** with SC in the absence of O_2 did not afford **7a** (refer to Table 2, entry 3). We also used another Lewis acid for the formation of **7**. However, the reaction of **4a** with the $TiCl_4/O_2$ system in CH_2Cl_2 gave **7a** in very low yield (entry 7).

Although oxidative coupling reactions of naphthols by several metal oxidants[1g,7] in the absence or presence of O_2 have been studied extensively, mixtures of dimeric, polymeric and quinoid compounds were usually generated. In addition, regioselective *ortho*/*ortho* coupling is more difficult to control in the reaction of NAPs such as **4d–e**.

In order to obtain **5e** as a synthetic intermediate for **3**, the *ortho*/*ortho* coupling reaction of **4e** with SC in the absence of O_2 was tried first, but the yield of **5e** was very low, partly because of the formation of a polymeric mixture. We then studied the reaction with the SC/O_2 system. In this reaction, *ortho*/*ortho*-coupled BNAP **5e** was obtained along with the trimeric furan **9e** without the formation of BNAPQ (entry 6). A noteworthy feature in the reaction with the SC/O_2 system is the difference between **4a** and **4d**, i.e., the formation of **7a** and **9d** having different frameworks. It appears that the formation of **7** requires electron-rich NAP having a methoxy group on ring A, as shown in Figure 1.

Thus, we have established a facile and biomimetic synthesis of 3,3′-bijuglone (**1**),[1c] 3,3′-biplumbagin (**2**)[1d] and elliptinone (**3**)[1e] from the corresponding **7a**, **7b** and **5e**, prepared by means of the reactions of NAPs with the SC/O_2 system.

To throw light on the formation of **6** and **7** in the reactions of **4a–b** with the SC/O_2 system in CH_2Cl_2, the reactions of **5a** with SC/H_2O_2 (hydrogen peroxide) and SC/O_2 reagent systems in CH_2Cl_2 were examined. In both cases, **6** and **7** were obtained (Table 1, entries



Scheme 1.

10–11). These results suggest the participation of H_2O_2 or O_2. In addition, the present reaction of **4** (1 mmol) involves a catalytic cycle of SC (0.25 equiv.) in all cases. Furthermore, there are a number of reports on the generation of H_2O_2 via hydroperoxy radical ($HO_2\cdot$) by reduction of O_2 in aprotic solvents in the presence of Brønsted acids such as phenol and perchloric acid ($HClO_4$) as proton sources by means of chemical and electrochemical methods.[8]

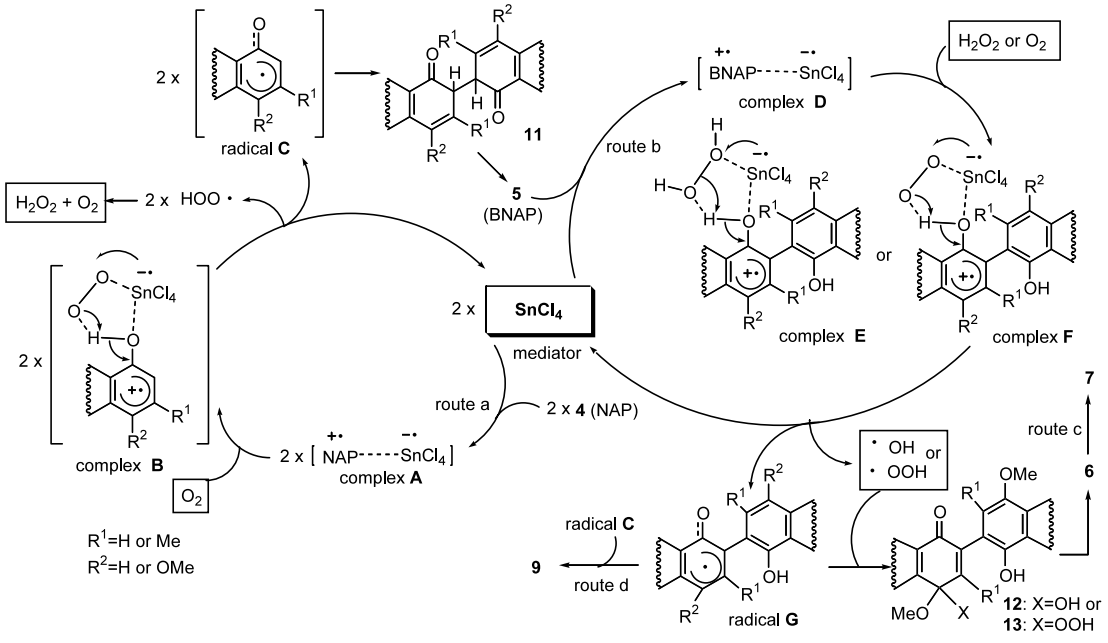
The above results and information allow us to propose a mechanism for the oxidative reaction of NAP with SC in the presence of O_2 as illustrated in Scheme 2. Here, O_2 can be incorporated into complex **A** to form the complex **B** in which the O_2 site receives one-electron transfer from the anion radical species (SC-·) and subsequent one-proton transfer from the NAP site to reform SC with the generation of the radical **C** and $HO_2\cdot$. Then, H_2O_2 and O_2 are generated by the disproportionation of two $HO_2\cdot$.[9] The complex **E** or **F** can be formed by the interaction of H_2O_2 or O_2 with complex **D** generated from SC and **5**, which is produced by *ortho*/*ortho* radical coupling of two **C**. In the reaction of **4a–b**, the quinones **6** can be formed via Fenton-like reaction[10a] of **E** or radical autoxidation type reaction[10b] of **F**. The formation of BNAPQ **7** takes place similarly (route c). On the other hand, the trimeric furan **9** is formed by *para*/*ortho* radical coupling between **G** and **C**, followed by oxidative radical chain reaction in the case of **4d–e** (route d).

SC plays an important role in the oxidative reactions of NAP in the presence of O_2. That is, it acts not only as a characteristic Lewis acid catalyst, but also as a mediator for the oxidative reaction. On the other hand, O_2 acts as one-electron acceptor from the anion radical species (SC-·) and a one-proton acceptor from NAP, and as an oxygen source for the formation of BNAPQ.

In our previous paper,[5] the formation of **8a** via **5a** was observed in the reaction of **4a** with SC using $MeNO_2$ as a solvent (Scheme 3 and Table 2, entry 1). This result prompted us to seek a simple method for DNF framework synthesis from NAP in one step.

In the second stage, further investigation of the reaction of **4**,[5,6] as well as **5** and **9**, with SC in the absence of O_2 was carried out. As shown in Table 2, **8a** and **8c** were obtained in satisfactory to high yield by the reactions of **4a** and **4c** with SC (1.3 equiv.) in CH_2Cl_2, and the reaction can be conveniently performed with NAP having a methoxy group on ring A. In addition, the transformations of **4** to **8** proceeded stoichiometrically overall, while the formation of **5** proceeded with a catalytic cycle of SC (entries 2, 3). On the other hand, no reaction of **4d**, which lacks the methoxy group, occurred in CH_2Cl_2. In contrast with this result, the reaction of **4d** in $MeNO_2$ in place of CH_2Cl_2 gave **8d** and **5d** (entry 6), and similar reaction for 15 h afforded **10**, with the disappearance of **4d** (entry 7). However, polymeric compounds were formed in both cases. The trimer **9** could be easily converted to the corresponding furans **10** (Scheme 1). The different yields of **8** in the present reactions are a consequence of the structural differences between **4a–c** and **4d**: a methoxy group on ring A is considered to activate the NAP ring for the formation of the EDA complex with SC, and to inhibit the production of polymeric compounds, including **10**, by reaction at the substituted position (R^2 position).

The formation mechanism of **8** from **4** can be rationalized in terms of the biaryl coupling of two radicals **C** via the EDA complex **A** of **4** with SC[5] and subsequent ring closure of the resulting **5** to form the DNF ring, based on the results listed in entries 8–10 (refer to Scheme 2). Although the exact mode of ring closure is not clear, we believe that it may proceed via radical

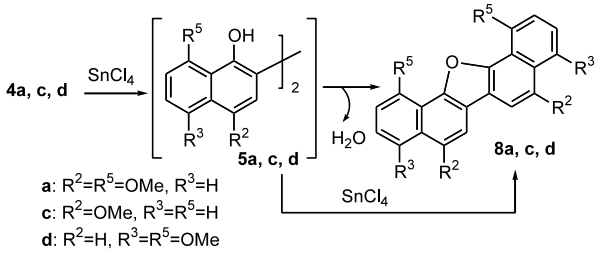


Scheme 2. Proposed mechanism for oxidative reaction of 1-naphthols with $SnCl_4$ in the presence of O_2.

Table 2. Reactions of naphthols with $SnCl_4$ in the absence of O_2[a]

Entry	Naphthol	Solvent	Time	Product (yield[b])	
				8	**10**
1	**4a**	$MeNO_2$	0.8	60	–
2	**4a**	CH_2Cl_2	56	92	–
3[c]	**4a**	CH_2Cl_2	96	14	–
4	**4c**	CH_2Cl_2	65	84	–
5	**4d**	CH_2Cl_2	65	No reaction	
6[d]	**4d**	$MeNO_2$	4.3	8	–
7[e]	**4d**	$MeNO_2$	15	Trace	9
8	**5a**	CH_2Cl_2	2	98	–
9	**5c**	CH_2Cl_2	63	91	–
10[f]	**5d**	$MeNO_2$	7	29	–
11	**9d**	$MeNO_2$	1.5	–	82
12	**9e**	$MeNO_2$	1	–	80

[a] General procedure: the reactions were carried out using $SnCl_4$ (1.3 equiv.) with a stirring in argon-saturated solvent at 100°C under normal laboratory light in a sealed tube. Similar results were obtained in the dark.
[b] Isolated yield (%).
[c] Similar reaction with $SnCl_4$ (0.25 equiv.) gave **8a** along with **5a** (59%).
[d] **5d** was also obtained in 16% yield along with the recovered **4d** (24%).
[e] Disappearance of **4d** was observed.
[f] **5d** (14%) was recovered and polymer was formed.



Scheme 3.

pathways[11] involving the formation of H_2O (the naphthoxy radical-induced reaction), rather than nonradical pathways[2b] (the Lewis acid-promoted dehydration pathway) because of the formation of polymeric compounds (including **10**) as described above (entries 6, 7 and 10). In this step, SC is inactivated by the resulting H_2O. In the oxidative reaction with SC in the absence of O_2, CH_2Cl_2 and $MeNO_2$ used as solvents also act as one-electron and one-proton acceptors[12] from the anion radical species (SC-·) and NAP, playing the same role as that of O_2 described above. The different reactivities in CH_2Cl_2 or $MeNO_2$ may be based on the difference of one-electron accepting ability from the anion radical species (SC-·). Further investigation on the synthesis of balsaminones A possessing the DNF framework is in progress.

In conclusion, the above reactions of NAP **4** proceed differently in the SC/O_2 system and SC system. For example, the reaction of **4a** with the SC/O_2 system afforded BNAPQ **7a** in good yield as the major product, while the reaction of **4a** with SC gave DNF **8a** in high yield. The SC-mediated oxidative reactions of NAP in the presence or absence of O_2 made it possible to control the synthesis in the direction of either the BNAPQ or the DNF framework.

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